The OECD QSAR Toolbox for Grouping Chemicals into Categories

## OECD (Q)SAR Toolbox v.4.4.1

An example illustrating RAAF scenario 6 and related assessment elements

#### **Outlook**

- Background
- Keywords
- Objectives
- Specific Aims
- Read Across Assessment Framework (RAAF)
- The exercise
- Workflow

#### Background

- This is a step-by-step presentation designed to take the Toolbox user through the workflow of a data gap filling exercise and assessing of the outcome whether the read-across prediction is scientifically acceptable or not;
- The read-across prediction will be justified by fulfilling all information requirements according to the Read Across Assessment Framework (RAAF).

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#### **Keywords**

**TARGET CHEMICAL -** chemical of interest.

**MODULE** – a Toolbox module is a section dedicated to specific actions and options (e.g. Profiling).

**WORKFLOW** – the use, in combination, of the different modules (e.g. prediction workflow: from input to report).

**PROFILER** - algorithm (rule set) for the identification of specific features of the chemicals. Several types of profilers are available, such as structural (e.g. Organic functional groups), mechanistic (e.g. Protein binding by OECD) and endpoint-specific (e.g. in vitro in vitro mutagenicity (Ames test) alerts by ISS) profilers.

**ALERT** - the profilers consist of sets of rules or alerts. Each of the rules consists of a set of queries. The queries could be related to the chemical structure, physicochemical properties, experimental data, comparison with the target or list with substances and external queries from other predefined profilers (reference queries).

**CATEGORY** – "group" of substances sharing same characteristics (e.g. the same functional groups or mode of action). In a typical Toolbox workflow, it consists of the target chemical and its analogues gathered according to the selected profilers.

**ENDPOINT TREE** – Endpoints are structured in a branched scheme, from a broader level (Phys-Chem properties, Environmental Fate and transport, Ecotoxicology, Human health hazard) to a more detailed one (e.g. EC3 in LLNA test under Human health hazard-Skin sensitization).

**DATA MATRIX** – Table reporting the chemical(s) and data (experimental results, profilers outcomes, predictions). Each chemical is in a different column and each data in a different row.

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#### **Objectives**

## This presentation demonstrates a number of functionalities of the Toolbox:

- Define target endpoint;
- Relevancy of profiles and data availability;
- Calculation of alert performance (AP) accounting for metabolism;
- Searching of analogues accounting for metabolism;
- Category consistency check;
- Selection of RAAF scenario;
- Filling in the report sections related to each read-across assessment element.

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#### **Specific Aims**

- To familiarize the user with the Read Across Assessment Framework (RAAF) and more specifically with Scenario 6;
- To introduce to the user the read-across assessment elements;
- To introduce to the user the report basket;
- To provide sufficient information allowing a scientific assessment of the outcome;
- To explain to the Toolbox user the rationale behind each step of the exercise.

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#### Read Across Assessment Framework (RAAF) Overview

- RAAF has been developed by ECHA as internal tool providing a framework for a consistent and structured assessment of grouping and read-across approaches under REACH.
- The outcome of the assessment is a conclusion on whether the readacross is scientifically acceptable or not
- The RAAF defines different scenarios for different read-across approaches
- Each scenario is associated with particular aspects (assessment elements, AEs) that are deemed crucial to the assessment
- Total six scenarios are available: two for analogue approach and four for category approach

#### Read Across Assessment Framework (RAAF) Criteria for the different RAAF scenarios

SCENARIO	APPROACH	READ-ACROSS HYPOTHESIS BASED ON	QUANTITATIVE VARIATIONS
1	Analogue	(Bio)transformation to common compound(s)	Property of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.
2	Analogue	Different compounds have qualitatively similar properties	Properties of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach.
3	Category	(Bio)transformation to common compound(s)	Variations in the properties observed among source substances. Prediction based on a regular pattern or on a worst-case approach.
4	Category	Different compounds have qualitatively similar properties	Variations in the properties observed among source substances. Prediction based on a regular pattern or on a worst-case approach.
5	Category	(Bio)transformation to common compound(s)	No relevant variations in properties observed among source substances and the same strength predicted for the target substance.
6	Category	Different compounds have qualitatively similar properties	No relevant variations in properties observed among source substances and the same strength predicted for the target substance

\*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf\_en.pdf

#### Read Across Assessment Framework (RAAF) Selection of RAAF scenario

- 1. Distinguish whether analogue or category approach is decided based on number (N) of analogues\*:
  - a) N of analogues  $\leq$  3 is Analogue approach (scenario 1-2)
  - b) N of analogues > 3 is Category approach (scenario 3-6)
- 2. To identify the basis of the read across hypothesis
  - a) (Bio)transformation to common compound(s) the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed
  - b) Different compounds have the same type of effect(s) the read-across hypothesis is that the organism is not exposed to common compounds but rather, as a result of similarity, that different compounds have similar (eco)toxicological and fate properties. These compounds may be the source and target substances themselves or one or more of their (bio)transformation products.
- 3. For a category approach (scenario 3-6) there is a need to take further account whether or not quantitative variations in the properties are observed among the category members:
  - a) There is quantitative variation in the (eco) toxicity when it is more than 1 log units\*\* (scenario 3 and 4)
  - b) Quantitative variation is not expected in the (eco) toxicity when it is less or equal to 1 log unit (scenario 5-6)

\* The threshold for number of analogues which distinguishes analogue from category approach is proposed by LMC \*\*The quantitative variation in the (eco)toxicity of 1 log unit is proposed by LMC due to empirically observations.

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#### • The exercise

• Workflow

#### **The Exercise**

- In this exercise we will predict a *Chromosomal aberration (CA)* of 3,5-Dichlorophenol [CAS# 591-35-5], which will be the "target" chemical.
- We will preliminary define the target endpoint;
- The category will be defined by DNA binding mechanism accounting for *in vitro* rat liver metabolism;
- The read-across approach will be used for the prediction. The readacross will be based on category approach expressed as common underlying mechanism for metabolites of source and target substances;
- Read-across assessment elements will be included to the report
- Examples for the possible content of each of AEs will be provided

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#### Workflow

The Toolbox has six modules which are used in a sequential workflow:

- o Input
- Profiling
- o Data
- Category Definition
- Data Gap Filling
- Report

#### **Input** Overview

- This module provides the user with several means of entering the chemical of interest or the target chemical.
- Since all subsequent functions are based on chemical structure, the goal here is to make sure the molecular structure assigned to the target chemical is the correct one.

#### **Input** Input target chemical by CAS#



#### **Input** Define target endpoint

Defining of the endpoint allows entering the endpoint of interest e.g. Chromosome aberration, EC3, LC50 etc., along with specific metadata information. Based on the metadata, different relevancy scores for profiles could be provided for same endpoint.

Calculation of alert performance (AP) is only possible if the target endpoint is preliminary selected.



#### **Input** Define target endpoint



#### **Input** Define target endpoint

Once the endpoint is defined along with its metadata, they appear in the endpoint tree and the corresponding row of the data matrix is yellow highlighted.

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					Input		Profiling	Data	Category defi	nition 🕨 Data	a Gap Filling	Report		
	Doc	ument				Sin	gle Chemical		C	hemical List		Search		Target Endpoint
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								Chromoson	ne aberration					
							Immunot	oxicity						
							Irritation	/ Corrosion						
							Neurotox	icity						
							Photoind	uced toxicity						
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#### **Profiling** Overview

- "Profiling" refers to the electronic process of retrieving relevant information on the target compound, other than environmental fate, ecotoxicity and toxicity data, which are stored in the Toolbox database;
- "Profiling" module contains all the knowledge in the system coded in profiling schemes (profilers);
- "Profilers" are a collection of empirical and mechanism knowledge (expertly derived) which could be used to analyse the structural properties of chemicals;
- The "profilers" identify the affiliation of the target chemical(s) to preliminary defined categories (functional groups/alerts);
- The "Profiling" module contains also observed and simulated metabolisms/transformations, which could be used in combination with the profiling schemes;
- The outcome of the profiling determines the most appropriate way to search for analogues, but they are also useful for preliminary screening or prioritization of substances;
- The "profilers" are not (Q)SARs, i.e. they are not prediction models themselves;
- Based on the "profilers' relevancy" (determined by the defined target endpoint), the most suitable once are getting colour highlighted.

### **Profiling** Profiling the target chemical

	Profiling     Category defin	01010 01 0 10100 hition Data Gap Filling	► Report	,	( 0 1 1 0 0 0 0 0 0 0 0 0 0
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O Documents	Filter endpoint tree Y	1 [target]			
▲ ✿ Document 2 # [C: 1;Md: 0;P: 0] CAS: 591355	Structure	HO			
	+ Structure info				
	Parameters				
Profiling methods	Physical Chemical Properties				
Options   Selecte	ronmental Fate and Transport				
f Select All Unselect All Inver	2 oxicological Information				
<ul> <li>Suitable</li> <li>DNA alerts for AMES_CA and MNT by OASIS</li> </ul>	an Health Hazards				
✓ DNA binding by OASIS					
Protein binding alerts for Chromosomal aberration by	ADME .				
A Plausible	Bioaccumulation				
Chemical elements					
DNA binding by OECD	Developmental loxicity / leratogenicity				
Groups of elements	Genetic Toxicity		1	Move to <b>Profiling</b> module:	
in vitro mutagenicity (Ames test) alerts by ISS	in Vitro		1.	Move to <b>Proming</b> module,	
Lininski Rule Oasis	Chinese konstan		2	Tick the checkboxes of a	all
OECD HPV Chemical Categories					
	Chromosome absorption			suitable profiles and simulate	or
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<ul> <li>Metabolism/Transformations</li> </ul>				(green nigniighted);	
Options 🖌 💙 🤇	Neurotovicity		3	Click Annly	
f Select All Unselect All	Photoinduced toxicity		5.	CICK Apply.	
A Suitable	Repeated Dose Toxicity				
Dissociation simulator					
Hydrolysis simulator (neutral)	Toxicity to Reproduction				
Observed Mammalian metabolism	Toxicity to Reproduction AOP				
<ul> <li>Unclassified</li> </ul>	Toxicokinetics, metabolisin and Distribution				

#### **Profiling** Profiling results

- 1) No DNA and Protein binding alerts for chromosomal aberration are identified in the target structure as a parent;
- 2) 3 metabolites are produced as a result of Rat liver S9 metabolism simulator;
- 3) General mechanistic DNA binding alerts are identified in the metabolites produced by the Rat liver S9 metabolism simulator.

#### See on the next slide

### **Profiling** Profiling the target chemical

QSAR TOOLEOX	Profiling     > Data     > Category definit	01010 01 0 10100 ► Data Gap Filling ► Report		× • • • • •
Profiling Custom profile				The OECD QSAR Toolbox for Grouping Chemicals into Categories
Appiy view New Delete				Developed by LMC, Bulgaria
Ocuments	Filter endpoint tree Y	i [target]		^
<ul> <li>Document 2</li> <li># [C: 1;Md: 0;P: 0] CAS: 591355</li> </ul>	Structure	HO		
	Irritation / Corrosion			
	- Neurotoxicity			
Profiling methods	Photoinduced toxicity			
Options   Selected  Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected Selected S	Sensitization			
T Select All Unselect All Invert				
✓ DNA alerts for AMES, CA and MNT by OASIS	Toxicity to Reproduction AOP			
✓ DNA binding by OASIS	Toxicokinetics, Metabolism and Distribution			
Protein binding alerts for Chromosomal aberration by C Plausible	Profiling		1 1	
Aquatic toxicity classification by ECOSAR	General Mechanistic			
Chemical elements	DNA binding by OASIS	No alert found		
Groups of elements				
in vitro mutagenicity (Ames test) alerts by ISS	DNA alerts for AMES, CA and MNT by	No alert found		
in vivo mutagenicity (Micronucleus) alerts by ISS	Protein binding alerts for Chromosom	No alert found	2	
OECD HPV Chemical Categories			<u> </u>	
	Hat liver S9 metabolism simulator	s metabolite(s)		
Metabolism/Transformations           Options ▲         1 Selected           f         Select All         Unselect All         Invert           ✓         Suitable         ✓         Suitable           ✓         Plausible         ✓         Plausible           ●         Dissociation simulator            ●         Hydrolysis simulator            ●         Observed Marmalian metabolism            ●         Observed Marmalian	DNA binding by OASIS	x AN2 x AN2 >> Michael-type addition, quinoid structures   x AN2 >> Michael-type addition, quinoid structures >> Qu   x Non-covalent interaction   x Non-covalent interaction >> DNA intercalation   x Non-covalent interaction >> DNA intercalation >> Quino   x Radical >> Radical mechanism via ROS formation (indirect)   x Radical >> Radical mechanism via ROS formation (indirect   x No alert found	3	
✓ Unclassified	Endpoint Specific	A set Manual Annual		
Autoxidation simulator Autoxidation simulator (alkaline medium)	DNA alerts for AMES, CA and	S x No alert found		
Hydrolysis simulator (acidic)	Protein binding alerts for Chro	> x ivo alert lound		× >

#### **Data** Overview

- "Data" refers to the electronic process of retrieving the environmental fate, ecotoxicity and toxicity data that are stored in the Toolbox;
- Data gathering can be executed in a global fashion (i.e., collecting all data for all endpoints) or on a more narrowly defined basis (e.g., collecting data for a single or limited number of endpoints).

#### **Data** Collecting experimental data



The OECD (Q)SAR Toolbox for Grouping Chemicals into Categories

#### **Data** Collecting experimental data

- Toxicity information on the target chemical is electronically collected from the selected dataset(s).
- It should be kept in mind that the search for data and analogues is performed only among the chemicals which are listed in the selected database(s), which in this example are *Genotoxicity OASIS and Toxicity Japan MHLW*.
- No experimental data related to the target endpoint are found (see next slide).

#### Data Collecting experimental data

QSAR TOOLEOX       Import         Data       Import         Export       Delete         Gather       Import         Import       UUCLID6         JUCLID6       Database Inventor	Profiling       Data       01010 01000       Filling         > Data       > Category definition       > Data Gap Filling
➢ Documents ▲ ② Document 2 # [C: 1;Md: 1;P: 0] CAS: 591355	Filter endpoint tree  Filter endpoint tree  I [target]  I [t
Databases      Detions     Detabases      Dotions     Select All     Unselect All     Invert About Options     Eve Instation ECETOC     Food TOX Hazard EFSA     GARD Skin sensitization     Genotoxicity Acarcinogenicity ECVAM     Genotoxicity pesticides EFSA     Human Half-Life     Kentenonce nege expression Grouden	<ul> <li>Physical Chemical Properties</li> <li>Environmental Fate and Transport</li> <li>Ecotoxicological Information</li> <li>Human Health Hazards</li> <li>Acute Toxicity</li> <li>A ADME</li> <li>Bioaccumulation</li> <li>Carcinogenicity</li> <li>Developmental Toxicity / Teratogenicity</li> <li>Genetic Toxicity</li> <li>Toy</li> </ul>
Keratinocyte gene expression Gwaudan     Karatinocyte gene expression LuSens     Micronucleus ISSMIC     Micronucleus OASIS     MUNRO non-cancer EFSA     REACH Skin sensitisation database (normalised)     Receptor Mediated Effects     Ren Dince Triv Fraunhofer ITEM     Inventories     Options	Implementation     M: Negative       Chromosome Absure     M: Negative       Chromosome aberration     Chromosome aberration       Immunotoxicity     Irritation / Corrosion       Neurotoxicity     Irritation / Corrosion       Sepecification     MISWADD

A pop-up message informs the user that there 1 experimental data found for the target chemical, click OK (1); However, no data is found for the target endpoint (2).

#### Category Definition Overview

- This module provides the user with several means of grouping chemicals into a toxicologically meaningful category that includes the target molecule.
- This is the critical step in the workflow.
- Several options are available in the Toolbox to assist the user in refining the category definition.
- In this case no DNA alert is identified in the target structure, but in its metabolites produced after *in vitro* rat liver metabolic activation. Based on that the analogues will be searched accounting for *in vitro* rat liver metabolism. In this way the target chemical and the identified analogues will have similar metabolic pattern (see the next slides).

### **Category Definition**

# Searching for analogues accounting for *rat in vitro* metabolism

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k Input		► Report	₩.
Critery rize	Category consistency Category elements		The OECD QSAR Toolbox for Grouping Chemicals into Categories Developed by LMC, Bulgaria
Doc. 2	Filter endpoint tree		^
A Socument 2 # [C: 1;Md: 1;P: 0] CAS: 591555	Structure	C Select metabolism Options   f Select All  Documented	- C X 0 Selected Unselect All Invert
	Structure info  Parameters  Physical Chemical Properties  Physical Chemical Properties  Ecotoxicological Information  Chuman Health Hazards	Observed Mammalian metabolism           Observed Microbial metabolism           Observed Rat In vivo metabolism           Observed rat liver metabolism with quantitative data           Observed Rat Liver S9           Microbial metabolism           ✓ Simulated           Autoxidation simulator	
Organic functional groups     Options      Oselected     f Select All Unselect All Invert     Suitable     DNA alerts for AMES, CA and MNT by OASIS     DNA binding by OASIS     Protein binding alerts for Chromosomal aberration by OASIS	Acute Toxicity     ADME     Bioaccumulation     Carcinogenicity     Developmental Toxicity / Teratogenicity     Genetic Toxicity	Autoxidation simulator (alkaline medium) Dissociaton simulator Hydrolysis simulator (acidic) Hydrolysis simulator (acidic) Hydrolysis simulator (neutral) in vivo Rat metabolism simulator Hisrobiah metabolism simulator Hisrobiah metabolism simulator	
Plausible Aquatic toxicity classification by ECOSAR Chemical elements DNA binding by OECD Groups of elements in vitro mutagenicity (Ames test) alerts by ISS in vitro mutagenicity (Micronucleus) alerts by ISS Lipinski Rule Oase	in Vitro     Bacterial Reverse Mutation Assay ( 1/1     M: Negative     in Vitro Mammalian Chromosome Ab     Chinese hamster     With S9     Chromosome aberration	3	4
OECD HPV Chemical Categories Organic functional groups Organic functional groups (nested)	Immunotoxicity . Irritation / Corrosion		OK Cancel
Organic functional groups (US EPA) Organic functional groups, Norbert Haider (checkmol)	Photoinduced toxicity	L	
Proten binding by OASIS Struct US-57 Unclassif 2. Click <b>Define with</b> 3. Select Rat liver St 4. Click <b>OK.</b>	lefinition module; metabolism; metabolism simulator;		

#### Category Definition Searching for analogues accounting for *rat in vitro* metabolism

Grouping options (Rat line)	ver S9 metabolism s	imulator)		_		<	$\frown$
🖲 All queries 🔵 At least c	one						1
Chemical	Query		Criteria			$\exists /$	<b>_</b>
Parent	none ~	No criteria.					Gro gen scro
Metabolite 1	none none Parametric Profile	3					•
	none ~	No criteria.					
Metabolite 3						~	h A
		Air chemicais				2	for
Parent & Metabolites	none ~	No criteria.				Ī	crit
Alert performance							
Scales							
Calculate							
				ОК	Cancel		

*Grouping options* dialogue appears. It shows all the generated metabolites of the target chemical (use the scroll bar to see them). It has two subsections:

- (1) shows the parent and each of the generated metabolites. This allows defining different criteria for each structure when looking for analogues.
- (2) treats the parent and its metabolites as a whole.
   i.e. the criteria is provided for the whole package (parent & metabolites) but not for separate metabolites.

A drop down menu (3) is available in the column "Query" for each of the structures which allow setting the type of criteria for looking for analogues.

#### Category Definition Searching for analogues accounting for *rat in vitro* metabolism

Grouping options (Rat liver S9 metabolism simulator) ×	
All queries      At least one	
Chemical Query Criteria	
Parent none v No criteria. alert 1	Target categories AN2 AN2 >> Michael-type addition, quinoid structures AN2 >> Michael-type addition, quinoid structures >> Quinones and Trihydroxybenzenes No alert found
Metabolite 1 none v No criteria. alert 2 alert 3	Non-covalent interaction Non-covalent interaction >> DNA intercalation <u>Non-covalent interaction &gt;&gt; DNA intercalation &gt;&gt; Quinones and Trihydroxybenzenes</u> Radical Radical >> Radical mechanism via ROS formation (indirect) Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes
Metabolite 2	Grouping with "DNA binding by OASIS" -      ×
All chemi 2 3 All chemi 2 3 Parent & Metabolites Profile · Profile: DNA binding by OASIS · Options: Edit	You have selected <and> from different hierarchy levels!       Selecting most informative level(s) will have the same results!       All categories       (N/A)       AE2       AE2 &gt;&gt; Electrophilc addition to c=c double bond</and>
Alert performance Scales	Combine profiles Invert result AND OR Strict Sort results OK
<ol> <li>Select a <i>Profile</i> option for the package "parent &amp; meta Select "<i>DNA binding by OASIS</i>" profile (to facilitate the Click <i>Edit</i>. The profiling results of the parent and its m Click <i>OK</i> to confirm the defined search criteria.</li> <li>Click <i>OK</i> on the appeared message.</li> </ol>	abolites"; esearch you could use the filter); etabolites based on DNA profiler;

## **Category Definition**

# Searching for analogues accounting for *rat in vitro* metabolism

Grouping options (Rat live)	ver S9 metabolism	simulator)	– 🗆 ×	
<ul> <li>All queries</li> <li>At least o</li> </ul>	one			At this step an alert performance
Chemical	Query	Criteria		At this step, an alert performance
Parent	Parent		^	could be calculated
HD	none ~	No criteria.	e Alert performance	options — 🗆 🗙
		-	Aggregation options	
Metabolite 1			Maximal	Categorical scale (ordinal)
	none ~	No criteria.	Iviaximai	
0			Chromosome aberrat	ion I (Oasis)
Metabolite 2	none ~	No criteria.	Chromosome aberrat	ion II (Japan 2
но			_	
Metabolite 3				
		All chemicals		
Parent & Metabolites	Profile ~	Profiler: DNA binding by OASIS ~ Options: Edit		3
	1			OK Cancel
Alert performance				
Calculate	4	<ol> <li>Click on Scales</li> <li>Select Chromo</li> <li>Confirm by OK</li> </ol>	s; some aber ;	ration I (Oasis) scale;
		4. Click <b>Calculate</b>	<b>?</b> .	

#### Category Definition Searching for analogues accounting for *rat in vitro* metabolism

Alert performance results		2			
Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Radical >> Radical >> Radical (mechanism via ROS formatio (indirect) >> Quinones and hydroxybenzenes <and>Nc valent interaction &gt;&gt; DNA rotaletn interaction &gt;&gt; DNA rotaletn interaction &gt;&gt; DNA valent interaction &gt;&gt; DNA valent interaction &gt;&gt; DNA valent interaction &gt;&gt; DNA valent interaction &gt;&gt; DNA intitydroxybenzenes <and>N alert found (DNA binding by OASIS)</and></and>	Positive 72 Negative 28	3.00%	Show chemicals With data(18) Show chemicals With data(7)	Show att(25)	<ul> <li>Once the calculation of AP is finished, a new window appears providing the following information:</li> <li>1) AP statistic accounting for all set criteria and all identified alerts in case of selected <i>profile</i> query.</li> <li>2) AP statistic for each of the searching criteria (i.e. for each of the alerts)</li> <li>3) Percentages of different data (positive/negative) and number of chemicals used for the statistic. The user is also able to see the corresponding chemicals (the parent chemicals are shown, only).</li> </ul>
Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Radical >> Radical mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes (DNA binding by OASIS)	Positive 74 Negative 25	1.07%	Show chemicals With data(20) Show chemicals With data(7)	Show all(27)	Image: Constrained and the second and the s
Using of "Rat liver S9 petabolism simulator" Combined parent and products requirements: Non-covalent interaction >> DNA intercalation >> Quinones and Trihydroxybenzenes (DNA binding by OASIS)	Positive 74 Negative 25	1.07%	Show chemicals With data(20) Show chemicals With data(7)	Show all(27)	$\begin{bmatrix} 127\\ 129\\ 214\\ 200\\ 129 \\ 214\\ 200\\ 200\\ 200\\ 200\\ 200\\ 200\\ 200\\ 20$
Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: AN2 >> Michael- type addition, quinoid structures >> Quinones and Trihydroxybenzenes (DNA binding by OASIS)	Positive 74 Negative 25	5.93%	Show chemicals With data(20) Show chemicals With data(7)	Show all(27)	The performance shows that the <i>Quinones and</i> <i>Trihydroxybenzenes</i> alert has very high predictability with
Using of "Rat liver S9 metabolism simulator" Combined parent and	Positive 33	.06% 4	Show chemicals With data(119)	, ,	respect the defined endpoint and selected databases. After analyzing the provided information close the window (4).

L Calculation of alert performance create a specific report item stored in the so-called Report basket.
### Report basket - overview

- The specific report items are collected during the workflow or from external modeling sources.
- All items are stored in the "*Report basket"* and can be used in the report to support or justify the consistency of a category.



## **Category Definition**

# Searching for analogues accounting for *rat in vitro* metabolism

Grouping options (Rat live)	ver S9 metabolism s	imulator)	-		×
All queries At least o	ne				
Chemical	Query	Criteria			
Parent is	none ~	No criteria.			
Metabolite 1	none ~	No criteria.			
Metabolite 2	none ~	No criteria.			
Metabolite 3					~
		All chemicals			
Parent & Metabolites	Profile ~	Profiler: DNA binding by OASIS V Options: Edit			
Alert performance				C	
Scales Calculate					1
			OK	Can	icel

After closing the *Alert performance* window, click **OK** (1) in Grouping options window to execute the search. The Toolbox system will search within the selected database for chemicals having the same metabolic pattern with respect to *DNA binding by OASIS profiler* as the target chemical.

### **Category Definition** Searching for analogues accounting for *rat in vitro* metabolism

26 chemicals (out of 408 chemicals) with 33 experimental results are identified fulfilling the searched criteria The result might be different, in case other selection of databases and grouping methods are used.



### Data Gap Filling Overview

- "Data Gap Filling" module give access to five different data gap filling tools:
  - $\circ$  Read-across
  - Trend analysis
  - (Q)SAR models
  - Standardized workflow
  - Automated workflow
- Depending on the situation, the most relevant data gap mechanism should be chosen, taking into account the following considerations:
  - Read-across is the appropriate data-gap filling method for "qualitative" endpoints like skin sensitisation or mutagenicity for which a limited number of results are possible (e.g. positive, negative, equivocal).
     Furthermore read-across is recommended for "quantitative endpoints" (e.g., 96h-LC50 for fish) if only a low number of analogues with experimental results are identified.
  - Trend analysis is the appropriate data-gap filling method for "quantitative endpoints" (e.g., 96h-LC50 for fish) if a high number of analogues with experimental results are identified.

• "(Q)SAR models" can be used to fill a data gap if no adequate analogues are found for a target chemical. Additionally, two workflows - Standardized and Automated have been developed in order to facilitate the users work. Once started, they follow the implemented logic and finish with prediction. The general differences between the two type of workflows are represented on the next slide.

### In this example we will use read-across approach.

The OECD (Q)SAR Toolbox for Grouping Chemicals into Categories

QSAR TOOLEOX	► Input	F Profiling → Data → C	Category definition				1	
Gap Filling	Workflow			1			T ft ir	he OECD QSAR Toolbox or Grouping Chemicals hto Categories
A set of the set o		Filter endpoint tree	ү 1 [target]	2 Possible data inco	onsistency —		8	9 10
<ul> <li>Document 2</li> <li># [C: 1]Md: 1;P. 0] CAS: 591355</li> <li>[C: 409;Md: 1808;P: 0] Group</li> </ul>	ing with metabolism: D	Structure	, Å	Metadata Endpoint Chromoso Metabolic activa With S9 (2 A Matter scale/unit	me aberration (26 chemicals; 33 data) ation 6 chemicals; 33 data) #	2	8	600
		Human Health Hazards  Acute Toxicity  ADME  Ricorgrupulation	8/12	Chromoso Chromoso Test organisms	me aberration I (Oasis) (15 chemicals; 22 data) me aberration II (Japan MHLW) (11 chemicals; 11 ( <b>species)</b> amster (26 chemicals; 33 data)	data)		
		Carcinogenicity     Carcinogenicity     Developmental Toxicity / Teratoge	enicity	✓ Type of method ✓ in Vitro (24	ammalian Chromosome Aberration Test (26 chem 5 chemicals; 33 data)	icals; 33 data)		
		in Vitro     Bacterial Reverse Mutation     in Vitro Mammalian Cell Micr     in Vitro Mammalian Chromos     in Vitro Mammalian Chromos	391/1580 M: Negative ronucl 9/9 some Ab	Select scale/unit to Chromosome a	use berration I (Oasis) [22 native data and 12 berration II (Japan MHLW) [11 native data and (	4	M: Negative	M: Positive M: I
¢	>	Undefined Metabolic	Ac 11/22	2				
🔿 Data Gap Filling Sett	ings		26/22	Converted data				
✓ Only endpoint relevant At this position: Select a cell with a rinid (bold) path		Without S9     Undefined Test organism     Mammalian Cell Gene Mutat	45/52 s (s 29/37 ion 15/15	10 from scale/unit C	hromosome aberration II (Japan MHLW)		M: Positive	
Automated workflows Standardized workflows	0 0	Immunotoxicity Irritation / Corrosion	1/1 30/47	M: Negative Chemicals 25/26; Data	32/33 OK	Cancel	M: Positive	
	<ol> <li>Go t</li> <li>Click</li> <li>Click</li> <li>Click</li> <li>Sele</li> </ol>	to <u>Data gap filin</u> k on the cell corr k <b>Read across</b> . ect scale <b>Chromo</b>	ng module; esponding somal ab	to target endp erration I (O	oint (the yellow ro ASIS) and click O	ow); K		

QSAR TOOLBO	IX	► Profiling	► Data ► Cat	egory definition	01010 01 0 10100 Data Gap Filling	► Report							
Gap Filling	Workflow Workflow Standardized Automated											The OECD QSAR To for Grouping Chem into Categories	olbox icals Bulgaria
	mente	Filter endpoint tree		💙 1 [target]	22	30	67	159	209	248	249	250 250	balgana
✓ Document 2     ✓ # [C: 1;Md: 1;P: 0] CAS: 59133     ✓ □ [C: 409;Md: 1808;P: 0] C     ✓ ■ [C: 26;Md: 335;P: 0]	nens 55 Grouping with metabolism: DNA   Enter GF(RA) <b> P: 0] Data usage options are cl</b>	Structure		ļ	2		°* ↓∕~⊙^*	Har Of Corg	нс		~0~	_0^	0
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			ithout S9 ined Test organism				Positive	M: Positive	M: Equivocal	M: Negative	M: Positive	M: Negative	M: I
		+ Mammalia	an Cell Gene Mutat	Choices			- OSIGIC						
		+ in Vivo		O Mode			Negative					M: Negative	
		Immunotoxicity	sion	O Lowest mode									
		- Neurotoxicity	SION	Highest mode     Madian	2								
		Photoinduced to	oxicity	Median									
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	>	Toxicity to Repro	oduction	Maximal									~
🔿 Data Gap Fill	ing Settings	<		O All		3							
Only endpoint relevant		Descriptors					ne aberration	n, based on 5 value	5		Sele	ct / filter data	^
At this position:		Descliption	-			OK Crast	1				Gap f	illing approact	
QSARs	0	Prediction	Ļ			Cancel						winters ( data	1
Automated workflows Standardized workflows	0 0		Positive		•	• •		• • • •	• •	•	Desc	nptors / data	L
In nodes below:			aberr								M	odel/QSAR	
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Automated workflows Standardized workflows	0 0		ö								C	)ata usage	
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				-			-			·	o not use tai	rget data for predic	tion
	1. Open <b>Ca</b>	lculation	n optiol	ns;								ccept prediction	
	2. Select D	ata usad	e and c	hoose `	<i>`Maxima</i>	/" (worst	t case	scenari	io is ar	plied):			
	3 Select C	K				(							
	J. Select U	'n.											

SAR TOOLBOX	문 ×	Data ► Category defin	01 01 10 nition > Data G	ap Filling	Report						۵ م م ه X چي	
Options  Profilers  Selected  f Select All Unselect All Invert About Options  APredefined  Database Affliction	Adjust options Target										The OECD QSAR To for Grouping Chen into Categories	oolbox nicals
Inventory Affiliation AN2 OECD HPV Chemical Categories AN2	2 >> Michael-type addition, qui 2 >> Michael-type addition, qui	Ŷ	1 [target]	22 S	ubcat	egoriz	zation	1	248	249	Developed by LMC 250	, Bulgaria
Substance type No a US-EPA New Chemical Categories No a ✓ General Mechanistic Non Biodeg BioHC half-life (Biowin) Non Biodegradation primary (Biowin 4) Parti	alert found covalent interaction covalent interaction >> DNA ir covalent interaction >> DNA ir		and the second s	-02°			44~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	44C		~0~	_0_	
Biodegradation probability (Biow Biodegradation probability (Biow Biodegradation probability (Biow Biodegradation probability (Biow Biodegradation probability (Biow DNA binding by OASIS DNA binding by OASIS	ical >> Radical mechanism via R ical >> Radical mechanism via R	Chromosome aberra 25/32 thout S9 24/30 ned Test organisms (spe 6/8 n Cell Gene Mutation A 3/3 6/10		M: Negative M: Negative M: Positive M: Negative	M: Positive M: Positive	M: Negative M: Positive M: Negative	M: Positive M: Positive	M: Positive M: Equivocal	M: Negative M: Negative	M: Positive M: Positive	M: Negative M: Negative M: Negative M: Negative	_ M: I M: I
Estrogen Receptor Binding Hydrolysis half-life (Ka, pH 7)(Hydrowin) Hydrolysis half-life (Ka, nH RYHydrowin) Options 4 Metabolisms 1 Selected	er from target by At least one categor All categories	sion xicity oxicity										
f         Select All         Unselect All         Invert         About         Options           Do not account metabolism         (25).         (25).         (25).         (25). <b>Observed Marmalan metabolism</b> (1) A         (1) A         (1) A	Analogues AN2  AN2 >> Michael-type addit AN2 >> Michael-type additic	duction AOP							2			1
Observed Rat In vivo metabolism (25) Observed rat liver metabolism with quantitative Observed Rat Liver S9 metabolism (2) A Simulated	AN2 >> Michael-type addit AN2 >> Shiff base formation AN2 >> Shiff base formation			Read-across pre Predicted: Posit	diction for Chrom	osome aberration	, based on 5 value	s		Sele	ct / filter data	Ŷ
Autoxidation simulator Autoxidation simulator (alkaline mediu Dissociation simulator (alkaline mediu Hydrolysis simulator (cacidic) Hydrolysis simulator (basic) 1) N	No alert found Non-covalent interaction Non-covalent interaction >> Non-covalent interaction >> Non-covalent interaction >>	Positive		•			• • • • • •	• •	•	Mark of Mark of Mark of Mark chemic	themicals by WS als by descriptor va ts by test condition	lue
nydroyse sindador (redda) in vivo Rat metabolism sinulator Microbial metabolism sinulator Rat iver 59 metabolism sinulator	Non-covalent interaction >> Radical	4 tive			•				•	Mark f Mark	ocused chemical focused points	
Tautomerism	ted 5 (20/25) Select different	-2	-1	0	1	2	3 4	5	6	Remo	ve marked data	

1. Open **Select filter data**; In order to refine the category and eliminated analogues by a different mechanism subcategorization process is applied:

- 2. Select *Subcategorize;*
- 3. Apply DNA binding by OASIS combined with Rat liver S9 metabolism simulator;
- 4. Remove analogues reacting by different mechanisms than the target chemical.

	<b>E</b>	Ê H	01010							>	0 5 6 0 0 <b>6</b>	
Subcategorization	– 🗆 X		finition Data Can F	illing	Penort						<u>Ş</u>	
Options   Profilers  Profilers  Select All  Predefined  Database Affiliation	Adjust options Target Michael addition				<u></u>					Tł fo in	e OECD QSAR Too r Grouping Chemi to Categories	olbox cals
Inventory Affiliation OECD HPV Chemical Categories Substance type US-EPA New Chemical Categories 4 General Mechanistic (AOT)Protein binding by OASIS v1 Biodeg BioHC half-life (Biowin)	Michael addition >> Michael addition >> Michael addition >> Michael addition >> No alert found		1 [target] 2:	Sul	ocateg	goriza	tion 2	_0^	261	300	332	Bulgaria
Biodegradation primary (Biowin 4) Biodegradation probability (Biowin 1) Biodegradation probability (Biowin 2) Biodegradation probability (Biowin 5) Biodegradation probability (Bi Biodegradation ultimate (Bio		Chromosome aberra 20/7 thout S9 19/7 ned Test organisms (spe 5, n Cell Gene Mutation A 3, 5,	6 N 5 N 5 N 3 N 8	: Negative : Negative : Positive : Negative	M: Negative M: Positive M: Negative	M: Positive M: Positive	M: Positive M: Equivocal	M: Negative M: Negative M: Negative M: Negative	M: Negative M: Positive	M: Positive M: Positive	M: Positive M: Negative	<mark>. M: I</mark> M: I
DHA binding by OECO Estrogen Receptor Sinding Hydrolysis half-life (Ka, pH 7)(Hydrowin) Hydrolysis half-life (Ka, nH 8)(Hydrowin) Options 4 Metabolisms 1 Selected	Oliffer from All cate	sion xicity xicity										
f         Select All         Unselect All         Invert         About         Options           Do not account metabolism         Documented         Observed Marmalan metabolism         Observed Marmalan metabolism	Analogues (19) Michael addi (19) Michael addi (3) Michael additi (19) Michael additi	duction AOF			· · · · 6 01				2			1
Observed rat liver metabolism with quantitative data     Observed Rat Liver S9 metabolism     Simulated     Autoxidation simulator     Autoxidation simulator     Dissociation simulator     Hydrolysis simulator	(12) Michael addi (12) Michael addi (18) Michael addi (18) Michael addi (16) No alert four (2) Schiff bace for	Positive		ead-across pred Predicted: Positiv		)	Dased on 5 values	0	•	Select Subc Mark che Mark chemicals	/ filter data ategorize micals by WS by descriptor valu	ie
Hydrolysis simulator (basic) 3 Hydrolysis simulator (neutral) in vivo Rat metabolism simulator Miscobial metabolism simulator	(3) Schiff base for (3) Schiff base for (1) SN1	250me				•		• •		Filter points Mark foc	by test conditions used chemical	
kat wer 59 metabolsm sinulator	Selected 14 (6/20)	4	-1	0	1	2	3	4	5	Mark fo	cused points marked data	
1. Open <b>Sel</b> 2. Select <b>Su</b>	ect filter	data; rize;			log	Kow				Ac	ept prediction	×
3. Apply DN/ <b>4. Remove</b>	3. Apply DNA binding by OECD combined with Rat liver S9 metabolism simulator; <b>4. Remove</b> analogues reacting by different mechanisms than the target chemical											



### **Data Gap Filling** Apply Category consistency elements

QSAR TOOLEOX	Profiling Category consistency	Data Category definition	and Filling → Report 1	The OECD QSAR Toolbox for Grouping Chemicals into Categories
Define Define with metabolism Subcategorize Combine Clustering	Category elements Filter endpoint tree Structure	Category consistency wizard     Wizard pages	- C X The physicochemical similarity within a category can be assessed by using calculated parameters and experimental physicochemical data available in the Toolbox.	Developed by LMC, Bulgaria
C (C 6/Md: 76/P: 0) Subcategorized:	Immunotoxicity Irritation / Corro Neurotoxicity Photoinduced to Repeated Dose T Sensitisation Toxicast Toxicity to Repro Toxicity to Repro Toxicity to Repro Profiling Profiling	Physicochemical similarity Structural similarity Mechanistic similarity (Eco)tox experimental data Options	2//3/D parameters  4 Parameters  2 D Boiling point log Kow Molecular Weight Vapor Pressure (Antoine method) Water Solubility  Add / Remove  Physico-chemical data  4 Physical Chemical Properties Boiling point 4 Partition Coefficient:	
Organic functional groups           Options         0 Selected           f         Select All         Unselect All           Suitable         o         Invert           Statiable         o         Select All           DNA binding by OASIS         DNA binding by OASIS         o           Protein binding alerts for Chromosomal aberration by OASIS         Protein binding alerts for Chromosomal aberration by OASIS           Plausible         Aquatic toxicky classification by ECOSAR         Cherrical elements           NA binding by OECD         Groups of elements         n votro mutagenicky (Airconucleus) alerts by ISS           n wor mutagenicky (Airconucleus) alerts by ISS         Decomposition of transition of transition of transition of transition of transition of transition of transitional groups (ID SER4)         Organic functional groups (ID SER4)           Organic functional groups (ID SER4)         Organic functional groups (ID SER4)         Organic functional groups (ID SER4)           Organic functional groups (ID SER4)         Organic functional groups (ID SER4)         Organic functional groups (ID SER4)	Descriptors Prediction	2.8 3 Active descriptor X	Add / Canol/Water Vapour pressure Water solubility Add / Remove 3.2 3.4 3.6 3.8 4 4.2 4.4 4.6 4.8	Select / filter data  Subcategorize  Mark chemicals by WS  Mark chemicals by descriptor value Filter points by test conditions Mark focused chemical  focused points pre-marked data crexisting marks  Accept prediction

After subcategorization process go back go the <u>Category definition</u> module (1) and apply Category elements<sup>\*</sup> (2). No different selection than the default is needed – click OK (3). Once the category elements are applied Accept prediction (4).

\*For more information on category elements see Tutorial TB 4.4. Category consistency

### **Report** Overview

- The report module allows generating a report for predictions performed within the Toolbox.
- The report module contains a predefined report template which users can customize.
- Additionally specific RAAF scenario could be chosen. Selection of one of the scenarios will append automatically the related assessment elements (AE) related to the corresponding report sections.
- For fulfilling of the AEs' sections an information stored in the so called "report basket" will be of help (see next slides)

### Considerations for selection of RAAF scenario

To select the applicable RAAF scenario for assessment, the following aspect should be taken into account:

- 1) the type of approach applied analogue approach or category approach;
- the read-across hypothesis (bio)transformation to common compound or different compounds have the same type of effect(s)
- 3) For category approach whether quantitative variations in the properties are observed among the category members must be considered.



\*Read-Across Assessment Framework (RAAF) available at https://echa.europa.eu/documents/10162/13628/raaf\_en.pdf

### **Report** Selection of RAAF scenario

For the current example:

- 1) the type of approach applied category approach is used (threshold of >3 analogues);
- 2) the read-across hypothesis different compounds with common underlying mechanism;
- 3) For category approach no quantitative variations is observed among the category members

Based on that Scenario 6 was selected for the current example.



### **Report** Selection of RAAF scenario

	<ul> <li>Data</li> <li>▶ Data</li> <li>▶ Category definition</li> <li>▶ Data Gap Filling</li> <li>▶ Report</li> </ul>	
Categorize Categorize Categorize Categorize	Insistency Iements	for Grouping Chemicals into Categories Developed <u>by LMC, Bulgaria</u>
Occuments         Filter endpoint           ✓         Document 2         # [C: 1:Md: 12P. 0] CAS: 591355         Filter endpoint           ✓         Image: C: 26/Md: 335/9: 0] Grouping with metabolism: DNA         Structure           ✓         Image: C: 26/Md: 335/9: 0] Enter GF(RA)         Structure           ✓         Image: C: 26/Md: 335/9: 0] Data usage options are chan         Structure           ✓         Image: C: 26/Md: 335/9: 0] Data usage options are chan         Structure           ✓         Image: C: 27/Md: 263/9: 0] Subcatecareadired: DNA bit         Structure	int tree $\overrightarrow{\mathbf{v}}$ i [target] 332 333 335 337 338	
<ul> <li>Target</li> <li>They a mechan</li> <li>No qua endpoin</li> <li>Organic functional groups</li> </ul>	and four analogues are grouped as a result of Rat liver S9 II have common reactivity pattern with respect to DNA hism) antitative variation of category members is observed w int (CA) (all analogues have positive CA data) DNA binding by OECD 3 x Michael addi 3 x M	9 metabolism (n>3) interaction (common with respect to target
Options         0 Selected           f         Select All         Unselect All         Invert           Suitable         DNA binding by OASIS         Predic         Predic           DNA binding by OASIS         Protein binding alerts for Chromosomal aberration by OASIS         Predic           Plausable         Aquatic toxicity classification by ECOSAR         Chemical elements         DNA binding by OECD           Groups of elements         in vitro mutagenicity (Ames test) alerts by ISS         in vitro mutagenicity (Micronucleus) alerts by ISS           DiPAb binding droups         OECD HPV Chemical Categones         Organic functional groups (IS EPA)           Organic functional groups (US EPA)         Organic functional groups (US EPA)	tion Positive Read-across prediction for Chromosome aberration, based on 5 values Predicted: Positive Positive Negative 2.8 3 3.2 3.4 3.6 3.8 4 4.2 4.4	Select / filter data  Subcategorize  Mark chemicals by WS  Mark chemicals by descriptor value  Filter points by test conditions  Mark focused chemical  Mark focused points  Remove marked data  Class existion marker

### Report generation according to RAAF Scenario 6



1. Go to *Report* module;

2. Select a cell with prediction - "R: Positive";

3. Click the *Prediction* button.

The **Report wizard** appears. It consists of different sections related to the types of the report - **Prediction** (4), **Category** (5) and **Data matrix** (6). The content of each of these three sections could be customized in the **Customization** section (7); Check the box at the top to add **RAAF scenario** (8). Select **Scenario 6** from the drop-down menu (9).

### Report generation according to RAAF Scenario 6

AEs related to each scenario appeared automatically to the corresponding report section



### Report generation according to RAAF Scenario 6



Information can be included by clicking the **Add/Remove** button (1) located below the corresponding AE. The *Add/Remove* button invokes the so-called "*Report basket*" (2). The latter contain different items triggered by the actions of the user during the workflow (e.g. Alert performance calculation, applying of category elements, etc.). Additionally, new items (including items with external content) can be created (3).

Items with external content (text and picture) will be added for **AE 6.1: Compounds the test organism is exposed to** (see next slides).

### Report generation according to RAAF Scenario 6

#### Section: Category

Subsection: Category definition and members AE C.1: Substance characterization



One assessment element (AE C.1) (1) related to the characterization of the category members is included in the **Category definition and members** section. In order to add substance characterization select **Add/Remove** button (2) and check *Table of category members* item (3), which is generated during the workflow. If impurities/additives of the used analogues are available, they will be also included. The current analogues have no additives/impurities. Example on how the AE C.1. will look in the generated report is shown when click on **Preview** button (4).

### Report generation according to RAAF Scenario 6

Create new items

#### **Section:** Category

#### **Subsection:** Category definition and members **AE C.5:** Reliability and adequacy of the source study(ies)



Automatically generated

### Report generation according to RAAF Scenario 6

#### Section: Category

#### **Subsection:** Category definition and members **AE C.5:** Reliability and adequacy of the source study(ies)



### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Category definition and members **AE 6.1:** Compounds the test organism is exposed to

Customize report content and	appearance – 🗆 X							
Wizard pages								
Customization	⊙ 1.1. Category definition							
Customize report	$\odot$ 1.2. Category members							
Target and prediction	A 2 Drafiles (Metabolisms							
summary								
Prediction details (I)	Ust of profiles/metabolisms							
Prediction details (II)	AE 6.1: Compounds the test organism is exposed to							
Target profiles	Hint							
Angle promes	PURPOSE: In this scenario, it is claimed that different compounds have the same effects for the property under							
details	consideration. Such different compounds may be the source and target substances themselves and/or their							
Category	- the compounds to which the test organism is exposed (after administration of the source and the target							
Category definition	substances) have been established in the documentation; and - the provided evidence supports the explanation.							
and members								
Consistency check	Add / Remove							
Options	L							
Data matrix								
Options								
	Back Next Cancel Create report							

The possible example text that could be added to the **AE 6.1** is:

- Four source substances (B, C, D and E) are used to predict the property under consideration for Target A;
- Source substances (analogues) B, C, D and E have common reactivity pattern;
- Functionality that may cause chromosomal aberration by three different mechanisms for DNA interaction is identified in the metabolites of all category members;
- The primary group is defined based on "Quinones and Trihydroxybenzenes" accounting for *in vitro* Rat metabolism.

How to add the report item with external content is illustrated on the next slide:

The OECD (Q)SAR Toolbox for Grouping Chemicals into Categories

### Report generation according to RAAF Scenario 6

#### Section: Category

#### **Subsection:** Category definition and members **AE 6.1:** Compounds the test organism is exposed to



 $\times$ 

### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Category definition and members **AE 6.1:** Compounds the test organism is exposed to

Customize report content and approximation		
Wizard pages		
Customization Customize report Prediction		Example of how the example text will look in the generated report is shown below:
Target and prediction summary	<ul> <li>Original Stress Stress</li></ul>	Four source substances (B, C, D and E) are used to predict (text provided by user)
Prediction details (II) Target profiles Analogues selection details Category Category definition and members Consistency check	AE 6.1: Compounds the test organism is exposed to Wint PURPOSE: In this scenario, it is claimed that different compounds have the same effects for the property under consideration. Such different compounds may be the source and target substances themselves and/or their (bio)transformation products. It has to be assessed whether: <ul> <li>the compounds to which the test organism is exposed (after administration of the source and target substances themselves and/or their (bio)transformation products. It has to be assessed whether:</li> <li>the compounds to which the test organism is exposed (after administration of the source and target subside in the documentation; and</li> <li>the provided evidence supports the explanation.</li> </ul>	Four source substances (B, C, D and E) are used to predict the property under consideration for Target A; Source substances (analogues) B, C, D and E have common reactivity pattern; Functionality that may cause chromosomal aberration by three different mechanisms for DNA interaction is identified in the metabolites of all category members; The primary group is defined based on "Quinones and Trihydroxybenzenes" accounting for in vitro Rat metabolism.
Options Data matrix Options	Four source substances (B, C, D and E) are used to predict (text provided t Edit Preview	There are two options (1) for editing or preview the generated report item. How will look the text item in the report is shown on the right (2)
	Back Next Cancel Create report	

### Report generation according to RAAF Scenario 6

#### Section: Category

#### **Subsection:** Category definition and members **AE 6.1:** Compounds the test organism is exposed to

Wizard pages         Customization         Customize report         Prediction         Target and prediction summary         Prediction details (I)         Prediction details (I)         Prediction details (I)	
Customization       Image: 1.1. Category definition         Customize report       Image: 1.2. Category members         Prediction       Image: 1.3. Profiles/Metabolisms         Image: 1.3. Profiles/Metabolisms       Image: 1.3. Profiles/Metabolisms         Image:	
Customize report       © 1.1. Category definition         rediction       © 1.2. Category members         Target and prediction summary       © 1.3. Profiles/Metabolisms         Prediction details (I)       © List of profiles/metabolisms         © AE 6.1: Compounds the test organism is exposed to	
rediction <ul> <li>1.2. Category members</li> <li>1.3. Profiles/Metabolisms</li> <li>                  List of profiles/metabolisms</li></ul>	
Target and prediction summary <ul> <li>I.3. Profiles/Metabolisms</li></ul>	
summary       Ist of profiles/metabolisms         Prediction details (I)       Image: A E 6.1: Compounds the test organism is exposed to	
Prediction details (I) © AE 6.1: Compounds the test organism is exposed to	
Bradistian details (I)	
Target profiles	
Apploques selection In this scenario, it is claimed that different compounds have the same effects for the property under consideration.	Such
details different compounds may be the source and target substances themselves and/or their (bio)transformation product	cts. It has to
Category     - the compounds to which the test organism is exposed (after administration of the source and the target substance)	ces) have
Category definition	
and members	
Consistency check Add / Remove	
Options A Four source substances (B, C, D and E) are used to predict (text provided t Edit Pre	eview 🏦
Data matrix	
Options	
Back Next Cancel	

### The possible image that could be added to the **AE 6.1** is:

Target A	Source B	Source C	Source D	Source E
, Č	ģ	À.		
EC Number:2097	EC Number:2024	EC Number:2132	. EC Number:2004	. EC Number:2017.
591-35-5	95-95-4	933-75-5	58-90-2	87-86-5
High	High	High	High	High
"3,5-dichlorophe	"2,4,5-trichlorop	"2,3,6-trichlorop	2,3,4,6-tetrachlor.	"pentachlorophe.

How to add the image to the report is illustrated on the next slides:

### Report generation according to RAAF Scenario 6



In order to add picture to the report: click *Add/Remove (1)* then click *Create new* (2) in the *Report basket* window, click *Image provided by user* (3) and then select *OK* (4). New window appears where you can add your custom picture by Copy/Paste or browsing (5) to the directory in your PC where the desired picture is saved\*. Finally confirm by *OK* (6). The entered picture will appear in the *Report basket* under *External content* section and the check box will be ticked. Finally confirm by *OK* (7) in the Report basket. As result of this a new item will be added in the wizard under the AE 6.1.

\*In the current example a picture illustrating the target chemical marked as Target A and source substances (marked with Source from B to F) was prepared in

advançe oECD (Q)SAR Toolbox for Grouping Chemicals into Categories

April, 2020

### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** *Consistency check* 

**AE C.2:** Structural similarity and structural differences within the category

Customize report content and a	pppearance – C X	
Wizard pages		The possible example text could be added to the <b>AE C.2</b> is:
Customization Customize report Prediction Target and prediction summary Prediction details (I) Prediction details (II) Target profiles Analogues selection details Category Category definition and members Consistency check Options Data matrix Options	<ul> <li>2.1. Physicochemical similarity</li> <li>2.2. Structural similarity</li> <li>Structural similarity</li> <li>Comments on structural similarity</li> <li>AE C.2: Structural similarity and structural differences within the category</li> <li>Hint</li> <li>Add/Remove</li> <li>Structural similarity between Target substance A and (text provided by use Edit Preview )</li> <li>O AE C.3: Link of structural similarity and differences with the proposed regular pattern</li> <li>2.3. Mechanistic similarity</li> <li>2.4. Additional endpoints</li> <li>2.5. Other AEs</li> </ul>	<ul> <li>Structural similarity between Target substance A and five source substances (B, C, D and E) according to Str. similarity profiler is in the range of [28.6 – 76.2%]</li> <li>Target A and substances D, E have same functionalities with respect to OFG profiler</li> <li>Source substance B and C have same functionalities as target A, with exception of one group: Aromatic perhalogencarbons</li> <li>Appendix with similarity table and profile statistics for OFG profiler could be provided here (see next two slides):</li> </ul>
	Back Next Cancel Create report	

### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Consistency check

AE C.2: Structural similarity and structural differences within the category



### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Consistency check

**AE C.2:** Structural similarity and structural differences within the category

Back

Next

Cancel

Customize report content and a	ppearance – 🗆	×
Wizard pages		The possible report item containing image file could be added to the <b>AE C.2</b> (see slide 59 with instructions have to exact it).
Customize report	🕑 2.1. Physicochemical similarity	with instructions now to create it):
Prediction		
Target and prediction summary	Structural similarity     Commente on structural similarity	Appendix with profiling statistics based on OFG profiler could be added
Prediction details (I)		
Prediction details (II)	At C.2: Structural similarity and structural differences within the category	
Target profiles		Organic functional groups
Analogues selection details	PURPOSE: The aim of this AE is to verify that all category members indeed meet the criteria for structural similarities and allowed structural differences used for the category description. It has to be assessed whether: - the structural similarities identified apply to all category members: and	3 -
Category	- there are structural differences which are allowed within the category.	
Category definition and members	Add / Remove	
Consistency check	Table with calculated structural similarity	A President C C C C C C C C C C C C C C C C C C C
Options Data matrix	A Structural similarity between Target substance A and (text provided by use Edit Preview	
Options	• AE C.3: Link of structural similarity and differences with the proposed regular pattern	
	⊙ 2.3. Mechanistic similarity	
	🕑 2.4. Additional endpoints	
	⊙ 2.5. Other AEs	

Create report

### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Consistency check

**AE C.3:** Link of structural similarity and differences with the proposed regular pattern

Customize report content and a	ppearance – 🗆 X	
Wizard pages		The possible content of text added to the <b>AE C.3</b> is:
Customize report	⊙ 2.1. Physicochemical similarity	
Prediction Target and prediction	Structural similarity       Structural similarity	No alerts related to chromosomal aberration have been identified in the
Prediction details (I)	<ul> <li>Comments on structural similarity</li> <li>AE C.2: Structural similarity and structural differences within the category</li> </ul>	structures of the target and the source
Target profiles Analogues selection details Category Category definition and members Consistency check Options Data matrix Options	<ul> <li>AE C.3: Link of structural similarity and differences with the proposed regular pattern</li> <li>Hint</li> <li>PURPOSE:</li> <li>It has to be assessed whether:         <ul> <li>the documentation provides an explanation why the category members should behave in a predictable manner (e.g. based on no absorption due to molecular-weight considerations, or lacking reactivity towards biological material, regular pattern in increasing strength of effect due to kinetic differences);</li> <li>it is likely that all category members follow the proposed explanation and where the boundaries of the category are in this reset, and</li> <li>the provided evidence supports the explanation.</li> </ul> </li> <li>Add / Remove</li> <li>2.3. Mechanistic similarity</li> <li>2.4. Additional endpoints</li> </ul>	<ul> <li>Target and analogues are activated as a result of in vitro S9 metabolism simulator by generating "Quinones and Trihydroxybenzenes";</li> <li>In this respect, the structurally defined category from target (A) and four source substances (B, C, D, E) have common reactivity pattern of generated <i>in vitro</i> S9 metabolites.</li> </ul>
	Seck Next Carel Contemport	

The OECD (Q)SAR Toolbox for Grouping Chemicals into Categories

### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Consistency check

**AE 6.2:** Common underlying mechanism, qualitative aspects

Customize report content and a	appearance – 🗆 X	
		The possible example text for <b>AE 6.2</b> is
Wizard pages		
Customization Customize report Prediction Target and prediction summary Prediction details (I) Prediction details (II) Target profiles Analogues selection details Category Category definition and members Consistency check Options Data matrix Options	<ul> <li>O 2.1. Physicochemical similarity</li> <li>O 2.2. Structural similarity</li> <li>O 3.3. Mechanistic similarity</li> <li>O Mechanistic similarity</li> <li>O Mechanistic similarity</li> <li>O AE 6.2: Common underlying mechanism, qualitative aspects</li> <li>I with</li> <li>PURPOSE</li> <li>The hypothesis/justification has to explain how the compounds the test organism is exposed to lead to the same type of effects, it has to be assessed whether:</li> <li>I the is mechanism links the structures of these compounds under consideration with the possibility to predict qualitatively similar type of effects for the target substance for the property under consideration; and</li> <li>I there are provided evidence supports the explanation.</li> <li>M Target substance A and source substances B, C, D, E (text provided by user Reference)</li> <li>O 2.4. Additional endpoints</li> <li>O 2.5. Other AEs</li> </ul>	<ul> <li>Target substance A and source substances B, C, D, E react via a common underling mechanism according to <i>DNA binding by OASIS</i></li> <li><i>Quinones and Trihydroxybenzenes</i> functionality alert is identified in all category members after metabolic activation (see Appendix Metabolite/Profiling)</li> <li>Common mechanism is illustrated in Appendix Metabolites/Profiling</li> <li>Our assumption is that the toxic effect is based on <i>Quinones and Trihydroxybenzenes</i> functionality</li> <li>As a primary group is used the <i>Quinones and Trihydroxybenzenes</i> group presented with three different mechanism of actions, supported by the calculated alert performance</li> <li>The similarity with respect to the metabolic pattern could be seen in <b>AE 4.5</b>. above.</li> </ul>
	Back Next Cancel Create report	

### Report generation according to RAAF Scenario 6

#### Section: Category

Subsection: Consistency check

**AE 6.3:** Common underlying mechanism, qualitative aspects

Wizard pages         istomization         Customize report         ediction         rediction         action graph and prediction         summary         Prediction details (I)         Prediction details (I)         Prediction details (II)         Target profiles         Analogues selection         details         Category definition and members         Options         Add / Remove            A four source substance A and four source substance A and four source substance A and four source substance B and four	Wizard pages         ustomization         Customize report         rediction         Customize report         rediction         Target and prediction         summary         Prediction details (I)         Prediction details (II)         Target profiles         Analogues selection details (II)         Target profiles         Analogues selection details (II)         Consistency check         Options         Add / Remove         At a tait influence         A Taiget substance have based accurace substances (B, C, D and E) are guartation (S selected): Human Heath Hazards#Genet         Table with profiling results for "DNA binding by OECO"         Table with profiling results for "DNA binding by OECO"         Table with norbing results for "DNA binding by OECO"         Table with profiling results for "DNA binding by OECO"         Table with norbing results for "DNA binding by OECO"         Table with profiling results for "DNA binding by OECO"         Table with norbing results for "DNA binding by OECO"         Table with profiling results for "D			
Astomization       Options ▲       2 Selected         f       Select All       Unselect All       Invert         ediction       2.2. Structural similarity       Image: Select All       Unselect All       Invert         image: Select All       Unselect All       Invert       Image: Select All       Unselect All       Invert         image: Select All       Unselect All       Unselect All       Invert       Image: Select All       Unselect All       Invert         image: Select All       Unselect All       Unselect All       Invert       Image: Select All       Unselect All       Invert         image: Select All       Unselect All       Unselect All       Invert       Image: Select All       Unselect All       Invert         image: Select All       Unselect All       Invert       Image: Select All       Unselect All       Invert         image: Select All       With profiling results for "Drotein Inteabolsm ("Rat Iwer Selected: Human Heath Hazards#Genet       Image: Select All       Image: Select All       Invert       Image: Select All       I	ustomization       Customize report         Customize report       2.1. Physicochemical sin         rediction       2.2. Structural similarity         Target and prediction summary       2.3. Mechanistic similari         Prediction details (I)       2.4. Additional endpoint         Prediction details (II)       2.5. Other AEs         Prediction details (II)       Atalogues selection details (II)         Analogues selection details (II)       AE 6.3: Common underlyin         Options       AE 6.3: Common underlyin         Bud of the scenario, quantitative difference       Table with profing results for "Structura similarity         Category definition and members       Mint         Options       Add / Remove         Add / Remove       Ata Add / Remove         Add / Remove       Ata C.4: Consistency of effect         A Target substance have been tested accomentation established that the category gradetion of the consistence set of the performance       A target substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text proposed substance A and four source substance B, or L (text pr	Wizard pages	💽 Report basket	– 🗆 X
istomization       Select All       Usselect All       Invert         Customize report <ul> <li>2.1. Physicochemical sin</li> <li>2.2. Structural similarity</li> <li>2.3. Mechanistic similari</li> <li>2.3. Mechanistic similari</li> <li>2.4. Additional endpoint</li> <li>2.5. Other AEs</li> <li>2.5. Other AEs</li> <li>3. Ale 6.3: Common underlyin</li> <li>Alalogues selection details (I)</li> <li>Alaiogues selection details</li> <li>Analogues selection details</li> <li>Alai Analogues selection details</li> <li>Analogues selection details</li> <li>Alai Analogues selection details</li> <li>Alai Analogues selection details</li> <li>Alai Analogues selection details</li> <li>Alai Analogues selection details</li> <li>Alai Alai Members</li> <li>Consistency check</li> <li>Options</li> <li>Add / Remove</li> <li>Add / Remove</li> <li>Add / Remove</li> <li>Alai Alai Alai anatrix</li> <li>Options</li> <li>Add / Remove</li> <li>Alai Alai Alai Singue substance A and four source substances B. D. E. (text provide blace Alai Content</li> <li>A four source substance A and source substances A. and source substances A. and four source s</li></ul>	ustomization		Options 🖌	2 Selected
	⊘ AE C.6: Bias that influences	Customization Customize report Prediction Target and prediction summary Prediction details (I) Prediction details (II) Target profiles Analogues selection details Category Category definition and members Consistency check Options Data matrix Options	<ul> <li>Report basket</li> <li>Options J</li> <li>Select All</li> <li>Select All</li> <li>Select All</li> <li>Select All</li> <li>Select All</li> <li>Table with profiling</li> <li>2.2. Structural similarity</li> <li>2.3. Mechanistic similari</li> <li>2.4. Additional endpoint</li> <li>2.5. Other AEs</li> <li>AE 6.3: Common underlyin</li> <li>Hint</li> <li>PURPOSE:</li> <li>Under this scenario, quantitative different has to be assessed whether:</li> <li>Table with profiling</li> <li>Table with selected</li> <li>Tage substance A</li> <li>General content</li> <li>General content</li> <li>General content</li> <li>General cont</li></ul>	2 Selected     Unselect All     Invert     results for "Protein binding alerts for Chromosol     results for "Protein binding alerts for Chromosol     results for "Protein binding alerts for Chromosol     similarity accounting for metabolism ("Rat liver 5     d no.1 (mage provided b     neces (B, C, D and E) are u     d No.2 (mage provided b     and on (text prov     and four source substances has common (t

#### The possible text added for the **AE 6.3** is:

- Target substance A and four source substances has common reactivity pattern
- They all formed Quinones and Trihydroxybenzenes functionality as metabolites responsible for the toxicity effects
- Toxic effects of all source substances and target are supported by the identified additional genotoxicity data
  - see Data matrix file generated by prediction Report

Include the **Endpoint data variation** item stored in the report basket (2).

### Report generation according to RAAF Scenario 6

#### Section: Category

Subsection: Consistency check

**AE 6.4:** Exposure to other compounds than to those linked to the prediction

Customize report content and     Wizard pages Customization	appearance – – ×	The possible example text to added to the <b>AE 6.4</b> is:
Customize report Prediction Target and prediction summary Prediction details (I) Prediction details (II) Target profiles Analogues selection details Category Category definition and members Consistency check Options Data matrix Options	<form><ul> <li>Q. 2. Structural similarity</li> <li>Q. 3. Mechanistic similarity</li> <li>Q. 3. Mechanistic similarity</li> <li>Q. 3. Mechanistic similarity</li> <li>Q. 1. Additional endpoints</li> <li>Q. 5. Other AEs</li> <li>Q. 6. 1. Stromon underlying mechanism, quantitative aspects</li> <li>Q. 6. 4. topscure to other compounds than to hose linked to the prediction</li> <li>Q. in IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII</li></ul></form>	<ul> <li>Target substance A and all source substances (B-E) do not have DNA alerts based on the endpoint-specific profiler and are not responsible for the toxicity effects acting as parents.</li> <li>Alerts for DNA binding causing chromosomal aberration (Quinones and Trihydroxybenzenes alert) are identified in the metabolites of the target and the source substances after <i>in vitro</i> Rat liver S9 activation</li> <li>Our assumption is that the toxicity effect of the category members is caused due to formation of active metabolites rather than of the chemicals themselves.</li> <li>How to add the text is shown on slide 56.</li> </ul>

### Report generation according to RAAF Scenario 6

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#### Section: Category

**Subsection:** Consistency check

**AE 6.4:** Exposure to other compounds than to those linked to the prediction

Customize report content and appearance

Wizard pages		Example generated
Customization Customize report Prediction	<ul> <li>⊙ 2.1. Physicochemical similarity</li> <li>⊙ 2.2. Structural similarity</li> </ul>	Report basket     Options     f
Target and prediction summary Prediction details (I) Prediction details (II)	Image: State Stat	Category     Table with     Table with
Target profiles Analogues selection details	AE 6.4: Exposure to other compounds than to those linked to the prediction     Hint	Lable with Lable of ca Lable with Latable with Latable with
Category Category definition and members Consistency check Options Data matrix	PURPOSE: Other compounds than those linked in the hypothesis to the prediction may be formed via other (bio)transformation pathways or may be intermediates/metabolites of the identified pathway. In addition, the impurity profiles associated with the source and target substances may have an impact on the prediction. The other compounds may have been identified by the hypothesis, but not linked to the prediction. Another possibility is that the occurrence of such compounds has been entified by the assessing expert. It has to be assessed whether: 1 and the compounds that those linked to the prediction may be formed (e.g. via another (bio)transformation pathway or as termediates) or are present as impurities (see AE A-1); and indications are available that such compounds could influence the prediction of the property under consideration.	table with table with table with table with table with
Options	Add / Remove A Target substance A and all source substances (B-E) do (text provided by us Edit Preview 1 C AE 6.5: Occurrence of other effects than covered by the hypothesis and justification AE C.4: Consistency of effects in the data matrix AE C.6: Bias that influences the prediction	DNA binding Michael-typ quinoid stru Quinones ar Trihydroxyb DNA interca

#### on how the AE 6.4 will look in the d report is shown:

Unselect All

larger and prediction		Table with profiling results for	DNA alerts for AMES	, CA and MNT b lism ("Rat liver 9	y OASIS" 9 metaholism si	mulator" and "DN	A alerts for AMES	CA and N
summary	⊙ 2.4. Additional endpoints	Table with profiling results for	DNA binding by OAS	SIS"	nal aborration b	OASIS"	,	
Prediction details (I)	2.5 Other AFs	Table with profiling similarity ac	counting for metabo	lism ("Rat liver S	9 metabolism si	mulator" and "Pro	tein binding alerts	for Chror
Prediction details (II)	○ AE 6.3: Common underlying mechanism, guantitative aspects	Endpoint data variation (1 selection)	ted: Human Health ted: Human Health	Hazards#Genet Hazards#Genet Imm ("Pat liver (	ic Toxicity) ic Toxicity; Hum	an Health Hazards	#Acute Toxicity)	(6//)
Target profiles Analogues selection details <b>egory</b> Category definition and members Consistency check Options	<ul> <li>AE 6.4: Exposure to other compounds than to those linked to the prediction</li> <li>Hint</li> <li>PURPOSE:</li> <li>Other compounds than those linked in the hypothesis to the prediction may be formed via other (bio)transformation pathways or may be intermediates/metabolites of the identified pathway. In addition, the impurity profiles associated with the source and target substances may have an impact on the prediction. The other compounds may have been identified by the assessing expert. It has to be assessed whether:</li> <li>ther compounds that those linked to the prediction may be formed (e.g. via another (bio)transformation pathway or as termediates) or are present as impurities (see AE A.1); and</li> </ul>	A Table with profiling similarly ac     A Table with profiling similarly ac     A Table of category members     Table with calculated structure     Table with profiling results for     Table with profiling results for     Table with profiling results for     Table with profiling similarly ac     A Table with profiling similarly ac	sounding for metabo similarity Organic functional g Structure similarity <sup>*</sup> DNA binding by OEC US-EPA New Chemi counting for metabo	isin ("Rat liver 5 roups" D" cal Categories" lism ("Rat liver 5	9 metabolism si 9 metabolism si	mulator and "DNL ulator" and "DNL ulator" Pi	A binding by ASS A binding by ASS elect All nselect All wert review elete	3 tegor
n matrix	indications are available that such compounds could influence the prediction of the property under consideration.	Table summari	zing number o	f metabolit	es including	parent with	specific ale	<sup>rts</sup> 4
	Add / Remove	DNA binding by OASIS	P1 591-35-5 1	P2 87-86-5 1	P3 58-90-2 2	P4 933-75-5 1	P5 95-95-4 1	
	⊙ AE 6.5: Occurrence of other effects than covered by the hypothesis and justification	quinoid structures >>	1	1	2	1	-	
	⊘ AE C.4: Consistency of effects in the data matrix	Quinones and Tribydroxybenzenes						
	○ AE C.6: Bias that influences the prediction	DNA intercalation >>	1	1	2	1	1	

Select All

Add/Remove (1) button then check t item is stored in the report basket, during the actions performed in the section Profiling. Right click and select Preview DULLON (3). Tables summarizing the number of metabolite including the parent with the alerts is provided (4).

× 2 Selected

Invert

### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Consistency check

**AE 6.5:** Occurrence of other effects than covered by the hypothesis and justification

Customize report content and ap     Wizard pages	ppearance – — X	The possible example text to be added
Customization Customize report	⊙ 2.1. Physicochemical similarity	to the AE 6.5 is:
Prediction Target and prediction summary Prediction details (I) Prediction details (II) Target profiles	<ul> <li>2.2. Structural similarity</li> <li>2.3. Mechanistic similarity</li> <li>2.4. Additional endpoints</li> <li>2.5. Other AEs</li> <li>AE 6.3: Common underlying mechanism, quantitative aspects</li> <li>AE 6.4: Exposure to other compounds than to those linked to the prediction</li> </ul>	<ul> <li>The target substance A and source substances B, C, D, E have common reactivity pattern based on presence of Quinones and Trihydroxybenzenes functionality in the structures of their</li> </ul>
Analogues selection details Category Category definition and members Consistency check Options	<ul> <li>➢ AE 6.5: Occurrence of other effects than covered by the hypothesis and justification</li> <li>➢ Hint</li> <li>PURPOSE:</li> <li>It has to be assessed whether:</li> <li>- additional mechanisms than those identified in the hypothesis may be acting on the basis of mechanistic insights or derived from information in the data matrix, and</li> <li>- these additional mechanisms affect the prediction for the property under consideration.</li> </ul>	<ul> <li>metabolites;</li> <li>The Quinones and Trihydroxybenzenes functionality could cause toxicity effect by three different mechanisms for DNA binding;</li> </ul>
Data matrix Options	Add / Remove         A The target substance A and source substances B, C, D, (text provided by u         Edit       Preview         A The target substance A and source substances B, C, D, (text provided by u         Edit       Preview         A The target substance A and source substances B, C, D, (text provided by u       Edit         A The target substance A and source substances B, C, D, (text provided by u       Edit         A The target substance A and source substances B, C, D, (text provided by u       Edit         A E C.4:       Consistency of effects in the data matrix         A E C.6:       Bias that influences the prediction	<ul> <li>No other functionalities causing chromosomal aberration by DNA damage have been identified in the structures of the parents and metabolites.</li> </ul>
	Back Next Cancel Create report	

### Report generation according to RAAF Scenario 6

#### **Section:** Category **Subsection:** Consistency check **AE C.4:** Consistency of effects in the data matrix Customize report content and appearance $\Box \times$ Wizard pages The possible text to added to the **AE C.4** is: Customization 2.3. Mechanistic similarity Customize report ② 2.4. Additional endpoints Prediction 2.5. Other AEs Target and prediction The target substance A and the four source summary 🕑 AE 6.3: Common underlying mechanism, quantitative aspects substances (B, C, D, E) show indication for Prediction details (I) AE 6.4: Exposure to other compounds than to those linked to the prediction chromosomal aberration effect. Prediction details (II) ✓ AE 6.5: Occurrence of other effects than covered by the hypothesis and justification The latter is supported by the experimental Target profiles AE C.4: Consistency of effects in the data matrix data identified for CA effect (caused also by Analogues selection Hint details DNA damage) found for target and source PURPOSE: Category The category justification should include comparison of experimental data for the category members and a clear data matrix. substances. Category definition It has to be assessed whether: - a data matrix has been provided which lists the category members in a suitable order versus their experimental data (e.g. for and members REACH information requirements) and which identifies data gaps; Here could be provided also the data matrix Consistency check - the properties of category members across the data matrix are consistent in effects; this has to be assessed in the following dimensions snapshot or reference to the Data matrix report Options within the specific property which is under consideration for the prediction; - between the property under consideration and related properties (e.g. between 28-day and 90-day repeated-dose Data matrix (see next slide). toxicity studies; reproductive toxicity screening tests; and pre-natal developmental toxicity studies); Options - characteristics across all relevant properties (e.g. different reactivity towards genetic material may indicate different reactivity towards biological macromolecules which may influence the prediction for a 90-day repeated-dose toxicity study); - the effects reported for the property under consideration differ in strength for the source substance and whether a basis for this difference is provided; and - the underlying data support the provided conclusions and explanations. Add / Remove A The target substance A and the four source substances ... (text provided by L Edit Preview AE C.6: Bias that influences the prediction Back Next Cancel Create report

The OECD (Q)SAR Toolbox for Grouping Chemicals into Categories

### Report generation according to RAAF Scenario 6

#### Section: Category

**Subsection:** Consistency check

**AE C.4:** Consistency of effects in the data matrix


# Report

## Report generation according to RAAF Scenario 6

#### Section: Category

Subsection: Consistency check AE C.6: Bias that influences the prediction

Wizard pages         ustomization         Customize report         rediction         Summary         Prediction details (I)         Target profiles         Analogues selection details         details         Stargery         Category definition and members         Options         ata matrix         Options         ata matrix         Options         With the substances have been considered and why they have been discarded.         • Hint Bus to be assessed whether:         • It is information is biologically significantly different for relevant properties in comparison with the existing analogue(s); and         • there is readily-available information from these additional substance;         • this in fifteneses the confidence in the prediction (possibility of underestimation of hazard).         • there additional sture and bable information	Customize report content and a	ppearance — D									
Wizard pages         ustomization         Customize report         rediction         Target and prediction         summary         Prediction details (I)         Prediction details (I)         Target profiles         Analogues selection details (I)         Target profiles         Analogues selection details (I)         Category definition and members         Consistency check         Options         Target amatrix         Options         Target out the is readily-available information tow the source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s) have been considered and why they have been docarded;         • There are additional, structurally-similar substances;         • this information is biologically significantly different for relevant properties in comparison with the existing analogue(s); and         • the analogues are obtained based on a grouping accounting (text provide faced).											
ustomization       Customize report         rediction       Target and prediction         summary       Prediction details (I)         Prediction details (I)       2.3. Mechanistic similarity         Prediction details (I)       2.4. Additional endpoints         Target profiles       2.5. Other AEs         Analogues selection       AE 6.3: Common underlying mechanism, quantitative aspects         Analogues selection       AE 6.4: Exposure to other compounds than to those linked to the prediction         Attarget profiles       AE 6.5: Occurrence of other effects in the data matrix         Category definition and members       AE 6.5: Bias that influences the prediction         AE C.4: Consistency of effects in the data matrix       AE C.6: Bias that influences the prediction         Options       AE is to be assessed whether:       It has to be assessed whether:         It has to be assessed whether:       It has to be assessed whether:       It has to be assessed whether:         It has to be assessed whether:       It has to be assessed which are currently not used in the analogue approach and why they have been considered and why they have been used to map the field of potential source substance(s), which ather substances have been considered and why they have been there it readify-available information from these additional substances:         It has to be assessed whether:       It has confidence in the prediction (possibility of underestimation of hazard). </th <th>Wizard pages</th> <th></th>	Wizard pages										
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The possible example text which could be added to the **AE C.6** is:

- The analogues are obtained based on a grouping accounting for *in vitro* rat liver metabolism;
- All analogues having different metabolic pattern with respect to DNA interaction causing chromosomal aberration have been removed during the subcategorization process.
- The identified four analogues used in the read-across prediction have the common functional groups according to the OFG profiling scheme and the same reactivity pattern with respect to DNA interaction;

### **Report** Generation of report

After clicking on the *Create report* button, *Generated report files* window appears. It contains three types of files:

- **1. Prediction report** a PDF file containing the prediction information related to the target.
- **2. Category report** a PDF file containing information for the consistency of the final category (target plus used analogues)
- **3. Data matrix** a MS Excel file containing chemicals used for prediction along with their data for selected parameters, profiles and endpoint tree positions.

RAAF AEs are included in the second file. All generated files should be provided when submitting a prediction.



### **Report** Generated report files

rediction re	port				Category report							
	ti et								QSAR Toolbo	ox report for catego	ry	
QSAR Toolt	cordance with	on for single n RAAF scenari	o 6)		The selecters specified	ed RAAF sce I in the first	enario is page —	- E	(in accordanc	e with RAAF scenario 6	)	
Date: 14 Apr 2020 Author(s): Contact details:							<u>:</u>	1. Category definition	<u>!</u>			
	Townst info	metion						1.1. Category definit	ion			
	l arget information				Category name manually editable field							
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SMILES: 0 Oc1cc(Cl)cc(Cl)c1 0	CAS#: 591-35-5 Other: EC Numb	; per:2097149	"3,5-dich dichlorop ;phenol,	lorophenol; bhenol, 3,5- 3,5-dichlor	Covered (target) endpoint(s) - Human Health Hazards/Genetic Toxicity: Chromosome aberration, With 59, Chinese hamster, in Vitro Mammalian Chromosome Aberration Test, in Vitro							
Structure Cl			o-;3,5-di ol"	chloro-phen				Category hypothesis	a ucar		manually editable field	
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		Data	ma	itrix ren	nort			CAS	Name	SMILES	Structure	
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Predicted endpoint: Chromosome aben	ration; No effe	6		504.05.5	07.05.5	50.00.0	000 75 5	05.05.4	Pentachiorophenoi		u a	
specified; No guideline specified	Che	Chemical name		3,5-Dichlorophenol	Pentachlorophenol	chlorophenol, 2,3,4,6-	2,3,6-Trichlorophenol	2,4,5-Trichlorophenol				
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Data gap filling method: Read-across a	analysis Boi	iling point	*C	234	312	288	262	262			d.	
Summary: manually editable field	log	gKow		2.8	4.74	4.09	3.45	3.45			u	
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	Wa	ater Solubility	mg/L	204	3.09	17.9	103	114	2,3,4,6-		TOT	
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	Pro Usi sim pro	Propues used for Using of "Rat liver S9 metabolism simulator" Combined parent and products requirements: Radical >> Radical mechanism via ROS formation		Parent and 3 metabolite(s);; metabolite(s); nd AN2, AN2 >> Michael-type addition, al >>, type addition, quinoid structures >> Michael- type addition, quinoid structures >>	Parent and 4 metabolite(s);; Has all of the required categories: AN2, AN2 >> Michael-type addition, quinoid structures, AN2 >> Michael- type addition, quinoid structures >>	Parent and 5 metabolite(s);; Has all of the required categories: AN2, AN2 >> Michael-type addition, quinoid structures, AN2 >> Michael- type addition, quinoid structures >>	Parent and 3 metabolite(s);; Has all of the required categories: AN2, AN2 >> Michael-type addition, quinoid structures, AN2 >> Michael-type addition, quinoid	Parent and 4 metabolite(s); Has all of the required categor AN2, AN2 >> Michael-type addi quinoid structures, AN2 >> Micl type addition, quinoid structure			a a	
		Kapicai mechanism via ROS formation (indirect) >> Quinones and Trihydroxybenzenes <and>Non-covalent interaction &gt;&gt; DNA intercalation &gt;&gt; Quinones and</and>		Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent	Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent	Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation,	Structures >> Quinones and Trihydroxybenzenes, No alert found, Non-covalent interaction, Non-covalent interaction >> DNA intercalation, Non-covalent	Quinones and Trihydroxybenze No alert found, Non-covalen interaction, Non-covalent intera >> DNA intercalation, Non-cova				

The OECD (Q)SAR Toolbox for Grouping Chemicals into Categories

April, 2020

### **Congratulations!**

- You have now been introduced to the RAAF scenario;
- You have now been introduced to the *Report basket*.
- You have now been introduced to the AEs related to Scenario 6.
- Note, proficiency comes with practice!